Liver and Carrots—The Perfect Health Food

Vitamin A and Retinoids: An Update of Biological Aspects and Clinical Applications
Edited by M. A. Livrea
Basel: Birkhauser (2000). 312 pp. $175.00

Vitamin A is a crucial molecule throughout the life of an organism. Via its biologically active metabolite retinoic acid (RA), vitamin A is involved both in embryonic development and the maintenance of the differentiated state in the adult animal. With regard to the embryo, very severe abnormalities in multiple organ systems occur if vitamin A is removed from the maternal diet. In adults, studies conducted after the First World War in which vitamin A was removed from the diet of laboratory and farm animals demonstrated that dramatic changes in body tissues occurred, including the transformation of the mucous epithelia of the body into keratinizing epithelia. The most notable and widespread defect due to lack of vitamin A in the human population manifests in the eyes as night blindness, or more severely, xerophthalmia and childhood blindness. Clinically evident vitamin A deficiency affects an estimated 14 million people annually worldwide. Amazingly, we learn in this book in a chapter by J. A. Olsen that the ancient Egyptians recognized night blindness and treated it correctly by applying the juice squeezed from cooked liver to the eyes or by prescribing liver in the diet. However, this knowledge seems not to have been available to clinicians in more recent times because night blindness plagued armies throughout the nineteenth century. If only those clinicians had been fluent in ancient Egyptian heiroglyphics the course of history might have been different. Intriguingly, the administration of excess vitamin A to the adult results in equally characteristic changes in the differentiated state of tissues. RA is a highly potent teratogen when administered in excess to embryos, including humans. Thus, there is a great deal of nutritional and embryological data in the literature on vitamin A and RA.

Vitamin A and its derivatives, known as retinoids, have come to prominence in biology since the discovery of the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). RA binds these nuclear transcription factors (members of the steroid hormone superfamily of nuclear receptors) in order to alter the pattern of gene transcription. To determine which receptors and which pathways are responsible for the particular anatomical abnormalities described in the vitamin A deficiency studies alluded to above, these receptors have been singly and multiply mutated in genetically engineered mice, and the entire spectrum of deficiency abnormalities has been recapitulated. For example, the ventral half of the eye is missing and other ocular abnormalities are found in RARγ/RXRα mutants, persistent truncus arteriosus and other heart defects as well as hypoplastic lungs are seen in RARα/RXRα mutants, and kidney and ureter defects occur in RAR/RXRα mutants. Thus, there is also a large literature on the biological role of the retinoid receptors.

Due to the function of RA in maintaining the differentiated state of tissues and particularly the skin, it has become increasingly valuable in the treatment of more than 100 dermatological disorders and of various cancers. Probably the most well known of its uses is in the treatment of acute promyelocytic leukemia, where RA induces complete remission rates of 90%, not by cytotoxicity but by the induction of normal differentiation and a return to normal hematopoeisis. Other excellent examples of its efficacy include the suppression of premalignant lesions including oral leukoplasia, bronchial metaplasia, and cervical dysplasia. It is also effective in reducing the incidence of secondary tumors in the aerodigestive tract. Thus, there is a vast literature concerning retinoids in dermatology and cancer.

Therefore, any book which purports to keep the reader updated on this wide spectrum of subjects and this vast array of literature has a daunting task. The major reference work for the retinoids (*The Retinoids*, eds. M. B. Sporn, A. B. Roberts, and D. S. Goodman, eds., Academic Press) is a massive tome of nearly 700 pages, but was published in 1994 and clearly needs updating. Thus, there is a need for a continual supply of new books. Since that time there have been at least three other books which review this literature: *Vitamin A in Health and Disease* (R. Blomhoff, ed., Marcel Dekker Inc., New York, 1994); *Retinoids: Their Physiological Function and Therapeutic Potential* (G.V. Sherbet, ed., JAI Press Inc., Greenwich, CT, 1997); and most recently *Retinoids: The Biochemical and Molecular Basis of Vitamin A and Retinoid Action* (H. Nau and W. S. Blaner, eds., Springer Verlag, Berlin, 1999). So how well does this new book edited by M. Livrea perform in this daunting task?

The book seems to be a sequel to a previous volume entitled *Retinoids: From Basic Science to Clinical Applications* edited by Livrea and Vidali in 1994 (Molecular and Cell Biology Updates, Birkhauser Verlag, Basel). This previous volume was based on the proceedings of a conference and thus would not be expected to provide an in-depth coverage of topics in the retinoid field, as the content of conference proceedings books depends on who turns up and who provides a manuscript. One might expect that this new book, billed in the title as an update, also would not provide an in-depth coverage and indeed, it does not. The chapters are often quite brief and occasionally bizarre. So do not read it as a newcomer to the field hoping to get a broad introduction to the subject.

The biological aspects of the book are mostly reported by leading scientists in the field, but the coverage is very patchy. Enzymology, metabolism, regulation of blood levels,visual transduction and pharmacokinetics are described, but one could not use this book to learn about the biology of the RARs and RXRs or anything about the role of retinoids in the embryo. For example, there have been some exciting advances on the role of retinoids in hindbrain development, Hox gene expression, motoneuron development, heart development and vascularization, lung development, and the part that certain RA synthesizing enzymes play in terms of these processes, but no mention of these advances is to be found.

On the bright side, the majority of the book is devoted to clinical aspects and here there is a good deal of very

valuable information on subjects such as the vitamin A requirements in humans, retinoids and immunity, retinoid action in the skin and the use of synthetic retinoids and synthetic receptor agonists in medicine. These parts contain extremely valuable information for updating the latest clinical facts and figures on retinoids and photoaged skin (how to look young again), the treatment of acute promyelocytic leukemia (now with clear up rates of up to 94%), the treatment of a wide variety of cancers and the data on trials of β-carotene and cancer (now with data from more than 22,000 patients). A chapter on retinoids and infectious diseases summarizes the worldwide data on the fantastic results of decreasing child morbidity by vitamin A supplementation. This data comes from the Indian subcontinent, Africa, and South America where vitamin A supplementation results in a 30% decrease in morbidity and mortality from diseases such as diarrhea, measles, malaria, and HIV.

Unfortunately, many books of this type, either based on conferences or having multiple authors, can suffer from short chapters and incomplete coverage, as the limited range of chapters on retinoid biology in this book clearly exemplifies. However, the clinical aspects of the book are very valuable, so if you require an update on these aspects of retinoid research then I recommend you look in here.

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Gap Junctions in the New Millennium: More Than Pretty Pictures

Gap Junctions—Volume 30: Advances in Molecular and Cellular Biology
Edited by Elliot L. Hertzberg
(Series editor, E. Edward Bittar)
Stamford, CT: JAI Press (2000). 407 pp. $128.50

The scene: a laboratory at the moment the identity of a disease-linked gene is revealed. Unexpectedly, the gene is described as encoding a "connexin, gap junction protein." The researcher, only vaguely familiar with these terms, consults a general cell biology textbook. There they encounter a circa 1970 electron micrograph of a gap junctional plaque. Faced with this beautiful but almost *Antiques Roadshow*–worthy relic, s/he wonders whether much has happened in the field of gap junctions since the Nixon administration.

The answer, as reviewed in this volume edited by Hertzberg, is an unqualified yes. Moreover, the above scenario is not purely hypothetical. Mutations in connexin genes have recently been causally linked to several human diseases previously thought to be unrelated to gap junctions, including the X-linked form of Charcot-Marie-Tooth disease (the second most common inherited peripheral neuropathy), multiple types of hearing impairment (including the major form of nonsyndromic sensorineural recessive deafness), and the skin disorders palmoplantar keratoderma and erythrokeratoderma variabilis.

Gap junctions are collections of transmembrane channels that directly link the cytosols of two adjoining cells. They are present in almost all cell types of multicellular tissues in organisms ranging from mesozoa to humans, making them arguably the most ubiquitous and evolutionarily ancient form of intercellular communication in the animal kingdom. Hertzberg and coauthors (all leaders in the field) review recent progress in the identification and molecular characterization of the constituents of gap junctions, the determination of how gap junction channels are assembled and gated, and the elucidation of the myriad roles gap junctions play in vivo.

As discussed in the chapter by Beyer and Willecke, at least 15 members of the connexin family of gap junction proteins have been identified in vertebrates. With very few exceptions, each connexin has been shown to be capable of mediating diffusional intercellular transfer of ions and low molecular weight substances when expressed in either naturally gap junction–deficient cell types or in paired *Xenopus* oocytes depleted of endogenous connexins using antisense oligonucleotides. Some members of the connexin family are restricted to one or a very few tissues whereas others are widely distributed. Although the mechanisms that govern connexin expression remain incompletely understood, connexin mRNA levels are regulated in a connexin- and cell type–specific manner in response to many physiological and pathophysiological processes, including tissue differentiation, wound healing, carcinogenesis, and embryonic development. Connexin genes have not been identified in nonchordates. Instead, the major structural components of gap junctions in invertebrates appear to be members of a large family of proteins referred to as the innexins (see Stebbings et al., Mol. Biol. Cell *11*, 2459–2470, 2000 for a recent discussion). Although they share the same four-transmembrane domain topology, the primary sequences of connexins and innexins are unrelated. Given the many morphological and functional similarities between vertebrate and invertebrate gap junctions, this implies either independent but convergent evolution of innexins and connexins or their remarkably rapid divergence from a common ancestor.

The simultaneous presence of multiple connexin species within the same cell and their complex patterns of expression imply that the members of the connexin family are functionally distinct. As reviewed in the chapter by Verselis and Veenstra, direct proof of this contention has been obtained by systematically expressing connexin isotypes individually in the aforementioned gap junction–deficient systems. Such studies have revealed that each connexin forms channels with characteristic single channel conductance(s), cation/anion selectivity, and (depending somewhat on the cell type) distinct responses to regulators of channel gating. Connexin type–specific differences in junctional permeability have been observed with both microinjected gap junction tracers